applicants file a paper enlarging margins on some of the pages of the Specification. (A new Specification is enclosed, including enlarged margins; no new matter has been added in the new Specification.) At the time the Office Action was mailed, applicants had not yet filed an Information Disclosure Statement (IDS). The CPA was filed, on March 9, 2000, in an abundance of caution, so that an IDS (enclosed) could be submitted, to ensure that the record reflects the Examiner's consideration of the prior art, notwithstanding its marginal relevance, and despite its apparently having already been considered by the Examiner and found, properly, not to provide a basis for the rejection of any claims.

Briefly, the relationship between the claimed invention and the prior art is as follows. Over a decade ago, a compound, Halichondrin B, was isolated from a marine sponge and found to have anti-cancer properties. Since its isolation, Halichondrin B, and portions thereof, have been synthesized by others in the prior art.

The present inventors set out to design, synthesize, and test a family of compounds that shared structural features with a portion of the native Halichondrin B molecule, but which differed from it in several fundamental respects (which will be summarized below). When this project was begun, it was not known whether these compounds would have biological activity. It was also not known whether the compounds could be made; no compounds like them had been described in the literature, and the synthetic methods used to make native Halichondrin B and its fragments could not, because of the basic structural differences, be adapted to make the new compounds; entirely new synthetic pathways would have to be devised.

The Examiner in the parent application knew that the prior art had isolated Halichondrin B, that Halichondrin B had anticancer properties, and that the prior art had synthesized Halichondrin B. The specification of the parent application summarized these aspects of the prior art as follows:

> The invention relates to pharmaceutically active macrolides. Halichondrin B is a potent anticancer agent originally isolated

from the marine sponde *Halichondria okadai*, and subsequently found in *Axinella sp.*, *Phakellia carteri*, and *Lissondendryx sp.*

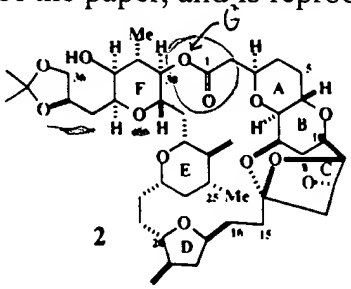
A total synthesis of Halichondrin B was published in 1992 (Aicher, T.D. *et al.*, *J. Am. Chem. Soc.* 114: 3162-3164). Halichondrin B has demonstrated *in vitro* inhibition of tubulin polymerization, microtubule assembly, beta^S-tubulin crossliking, GTP and vinblasting binding to tubulin, and tubulin-dependent GTP hydrolysis and has shown *in vitro* and *in vivo* anti-cancer properties.

Thus, the complete absence in the prior art of any suggestion to make the major changes in the structure of the Halichondrin B molecule memorialized in the present claims precluded a *prima facie* finding of unpatentability over the prior art.

Nonetheless, because the CPA was filed, on March 9, 2000, in order to ensure that the record reflect consideration of the prior art, applicants now take this opportunity to point out with more particularity the distinctions of the claims over the prior art references listed in the enclosed IDS.

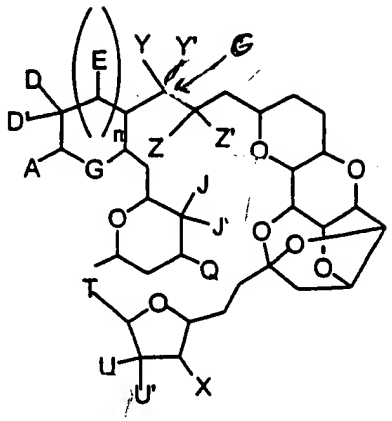
Horita *et al. (Tetrahedron Letters* 38(52):8965-8968, 1997)

In this paper, the authors report the synthesis of a portion (the "lactone portion") of the native Halichondrin B molecule (structure 1 of the paper); this lactone portion is shown as structure 2 on page 8965 of the paper, and is reproduced below:



Horita *et al.* structure 2, above, differs fundamentally in structure from the structure of generic claim 1 of the present application, which is reproduced below:

1. A compound having the formula:



wherein A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, said skeleton being unsubstituted or having between 1 and 10 substituents, inclusive, independently selected from cyano, halo, azido, oxo, and Q_1;

each Q_1 is independently selected from OR_1, SR_1, SO_2R_1, OSO_2R_1, NR_2R_1, $NR_2(CO)R_1$, $NR_2(CO)(CO)R_1$, $NR_4(CO)NR_2R_1$, $NR_2(CO)OR_1$, $(CO)OR_1$, $O(CO)R_1$, $(CO)NR_2R_1$, and $O(CO)NR_2R_1$;

each of R_1, R_2, R_4, R_5, and R_6 is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{6-10} aryl, C_{6-10} haloaryl, C_{6-10} hydroxyaryl, C_{1-3} alkoxy-C_6 aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{1-6} alkyl-C_{6-10} aryl, C_{6-10} haloaryl-C_{1-6} alkyl, C_{1-6} alkyl-C_{6-10} haloaryl, (C_{1-3} alkoxy-C_6 aryl)-C_{1-3} alkyl, C_{2-9} heterocyclic radical, C_{2-9} heterocyclic radical-C_{1-6} alkyl, C_{2-9} hydroxyheterocyclic radical, C_{2-9} heterocyclic radical-C_{1-3} alkylhydroxy, C_{2-9} heteroaryl, and C_{2-9} heteroaryl-C_{1-6} alkyl;

each of D and D' is independently selected from R_3 and OR_3, wherein R_3 is H, C_{1-3} alkyl, or C_{1-3} haloalkyl;

n is 0 or 1;

E is R_5 or OR_5;

G is O, S, CH_2, or NR_6;

each of J and J' is independently H, C_{1-6} alkoxy, or C_{1-6} alkyl; or J and J' taken together are $=CH_2$ or –O-(straight or branched C_{1-5} alkylene)-O-;

Q is C_{1-3} alkyl;

T is ethylene or ethenylene, optionally substituted with $(CO)OR_7$, where R_7 is H or C_{1-6} alkyl;

each of U and U' is independently H, C_{1-6} alkoxy, or C_{1-6} alkyl; or U and U' taken together are $=CH_2$ or –O-(straight or branched C_{1-5} alkylene)-O-;

X is H or C_{1-6} alkoxy;

each of Y and Y' is independently H or C_{1-6} alkoxy; or Y and Y' taken together are =O, $=CH_2$, or –O-(straight or branched C_{1-5} alkylene)-O-; and

each of Z and Z' is independently H or C_{1-6} alkoxy; or Z and Z' taken together are =O, $=CH_2$, or –O-(straight or branched C_{1-5} alkylene)-O-;

or a pharmaceutically acceptable salt thereof.

First, applicants note that structure 2 of Horita *et al.*, which, as is noted above, is a portion of the native Halichondrin B molecule, is a lactone (*i.e.*, a cyclic *ether*; see the atom in structure 2, above, labeled as "G," which is an oxygen), in contrast to the molecules claimed in the present invention, which are cyclic *ketones* (see the atom in the structure of claim 1, above, labeled as "G," which is in a position in this structure corresponding to position "G" of Horita *et al.*, and is a carbon). Second, the structure of the ring labeled as "F" in structure 2 of Horita *et al.* is simplified in the corresponding position in the structure of claim 1.

Kishi *et al.*, U.S. Patent No. 5,436,238; Stamos *et al.* (*J. Org. Chem. Soc.* 62:7552-7553, 1992); Kishi *et al.*, PCT WO 93/17690; Kishi *et al.* U.S. Patent No. 5,338,865; Gravalos *et al.*, EP 0572109A1

These references all disclose full or partial structures of the native Halichondrin B molecule, which all include the same structure as structure 2 of Horita *et al.*, above (*i.e.*, the lactone portion).

The fundamental structural differences between the claims and the prior art are not suggested in any prior art of which applicants are aware. It follows, of course, that nothing in the prior art would have suggested that the compounds of the invention, with their unprecedented structures, would exhibit the anti-proliferative biological activity applicants have observed for these compounds.

Just as significantly with respect to nonobviousness, the prior art contains no hint as to how the compounds of the invention could be synthesized. The synthetic methods described in Horita *et al.* and the Kishi references are specifically designed to yield the native lactone (or a molecule including the native lactone); see, *e.g.*, Horita *et al.*, who use a complex method referred to as "Yamaguchi macrolactonization of the seco-acid..." To make the cyclic ketones of the present invention, an entirely unrelated, unique, and complex synthetic pathway had to be designed, which included, *e.g.*, intramolecular

Williams ether formation (see page 8, line 28 of the specification).

CONCLUSION

It is submitted that all of the claims are in condition for allowance, and such action is requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: March 13, 2000

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